Synthesis, Crystal Structure and Antitumor Activity of Tectochrysin-6-sulfonate

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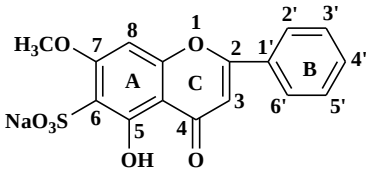
ABSTRACT In order to enhance water-solubility and biological utilization rate of tectochrysin, sodium 5-hydroxyl-7-methoxyflavone-6-sulfonate (**1**) was synthesized and its structure was identified on the basis of ^{1}H NMR, FT-IR and elemental analysis. 5-Hydroxyl-7-methoxyflavone-6-sulfonate was assembled with Ni(II) or Mn(II), hexaquanickel(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate (**2**) and hexaquamanganese(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate (**3**) were obtained and characterized by IR spectroscopy. The crystal structures of **2** and **3** were determined by X-ray single-crystal diffraction analysis. The results showed that **2** and **3** are isomorphous crystals and crystallize in monoclinic crystal system, space group *C*2/*c*. In **2** and **3**, the supramolecular structures are organized into hydrophilic and hydrophobic regions. Hydrophilic regions are generated by O–H···O hydrogen bonds among sulfonate groups, latticed water molecules and coordinated water molecules. The *π*-*π* stacking interactions assemble the flavone skeletons into columns and these columns form hydrophobic regions. The sulfonate groups play an important role as a bridge of the hydrophilic and hydrophobic regions as well as the inorganic and organic components. Three-dimensional networks of **2** and **3** are furnished by extensive array of hydrogen bonds, *π*-*π* stacking interactions and electrostatic interactions. The anti-proliferative activities of **1**～**3** *in vitro* against human leukemia cells K562 and human lung cancer cells A549 were evaluated by the standard MTT assay. The pharmacological activity results showed that the introduction of sulfonic acid groups enhanced the antitumor activity of tectochrysin.

Keywords: 5-hydroxyl-7-methoxyflavone-6-sulfonate; spectroscopic property; crystal structure; antitumor activity; DOI: 10.14102/j.cnki.0254-5861.2011-1791

1 INTRODUCTION

Tectochrysin (5-hydroxyl-7-methoxyflavone), a naturally wide distributed flavonoid, as one of the effective components of propolis[1], had many different biological activities such as anti-cancer[2], anti-oxidant[3] and

trypanocidal activity[4]. The solubility of flavonoid is poor and its biological utilization rate is low, so it is necessary to synthesize some water-soluble flavonoid derivatives in order to improve their possible biological activities. The introduction of a sulfonate group into flavonoid molecules can enhance their water-solubility and biological activities[5, 6]. We have synthesized some flavonoidsulfonates[7, 8], especially studied the biological activities of sodium 7,4′-dihydroxyisoflavone-3'-sulfonate[9] and sodium 4′-hydroxy-7-methoxyisoflavone-3′-sulfonate[10]. The results showed that the biological activities of flavonoidsulfonates are better as compared with the corresponding parent flavonoids. In this paper, sodium 5-hydroxyl-7-methoxyflavone-6-sulfonate (**1**, scheme 1) was synthesized, 5-hydroxyl-7-methoxyflavone-6-sulfonate was assembled with Ni(II) or Mn(II), and hexaquanickel(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate (**2**, $[Ni(H_2O)_6]$ $(C_{16}H_{11}O_4SO_3)_2 \cdot 4H_2O$) and hexaquamanganese(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate (**3**, $[Mn(H_2O)_6](C_{16}H_{11}O_4SO_3)_2 \cdot 4H_2O$) were obtained. The structure of **1** was established on the basis of ^{1}H NMR, FT-IR and elemental analysis. **2** and **3** were characterized by IR spectroscopy. The crystal structures of **2** and **3** were determined by X-ray single-crystal diffraction analysis. The antitumor activities of **2** and **3** against human leukemia cells K562 and human lung cancer cells A549 were evaluated by the standard MTT assay[11, 12].



Scheme 1. Chemical structure of 1

2 EXPERIMENTAL

2. 1 Materials and physical measurements

All the chemicals and solvents used for synthesis were of analytical grade available commercially and used without further purification. The sample was dried with 2K-82B vacuum drying oven. The infrared spectrum was recorded on a Nicolet 170SX FT-IR spectrophotometer with KBr pellets in the 4000～500 cm^{-1} region. The ^{1}H NMR Spectrum was recorded on a Bruker AM-300 spectrometer with TMS as internal reference and DMSO-d_6 as solvent. C and H contents were analyzed using a PE-2400 elemental analyzer. The crystal structures were determined with a Bruker Smart-1000 CCD diffractometer.

2. 2 Synthesis of 1

Tectochrysin (2.0 g) was slowly added to concentrated sulfuric acid (10 mL) with stirring. The reaction was maintained at room temperature for 15 hours. Then, it was poured into NaCl saturated aqueous solution (50 mL) and a yellow precipitate appeared. After 5 h, the precipitate was filtered and washed with NaCl saturated aqueous solution until the pH value of the filtrate was 7. The precipitate was recrystallized from an ethanol-water (V:V = 1:1) solution to afford **1**. It was dried at 105 ℃ for 10 h with vacuum drying oven. Yield = 75%. IR (cm^{-1}, KBr) *v*:

3467, 1644, 1606, 1486, 1447, 1206, 1145, 1098, 1046, 897, 809, 773, 686. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 13.13 (s, 1H), 7.56～7.87 (m, 5H), 6.78 (s, 1H), 6.52 (s, 1H), 3.89 (s, 3H). Anal. Calcd. for $C_{16}H_{11}NaO_7S$ (%): C, 51.89; H, 2.99. Found (%): C, 51.15; H, 3.21.

2. 3 Syntheses of 2 and 3

An aqueous solution of $Ni(NO_3)_2$ $6H_2O$ (10%, 5 mL) was mixed with aqueous solution of **1** (5%, 10 mL), obtaining **2** after 24 h. **2** was recrystallized from an ethanol-water (V:V = 3:1) solution. Green block crystals suitable for X-ray analysis were obtained by slow evaporation of the solvent for about 5 d at room temperature. Yield = 81%. IR (cm^{-1}, KBr) *v*: 3461, 1646, 1608, 1483, 1445, 1208, 1176, 1099, 1042, 898, 805, 770, 678.

The method for synthesis of **3** is similar to that of 2, differing only in replacement of $Ni(NO_3)_2$ $6H_2O$ with $MnSO_4$ H_2O. Yield = 85%. IR (cm^{-1}, KBr)*v*: 3460, 1643, 1596, 1486, 1446, 1201, 1182, 1099, 1043, 898, 811, 761, 684.

2. 4 X-ray crystallography of 2 and 3

A single crystal of **2** or **3** was mounted on a Bruker SMART-1000 CCD diffractometer equipped with a graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) for intensity data collection at 296(2) K. The structures were solved by direct methods with SHELXTL software package[13] and refined by full-matrix least-squares techniques. The non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located at the geometrically calculated positions and refined using a riding model. The final refinement converged to R = 0.0407, wR = 0.1077 for **2** and R = 0.0322, wR = 0.0717 for **3**. Details of crystal data collection and refinement are given in Table 1, and the selected bond lengths and bond angles in Table 2. More details about the crystallographic data have been deposited as supplementary materials.

Table 1. Crystal Data and Structure Refinement for 2 and 3

Compound	**2**	**3**
Empirical formula	$C_{32}H_{42}NiO_{24}S_2$	$C_{32}H_{42}MnO_{24}S_2$
Formula weight	933.49	929.72
Temperature (K)	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space Group	*C*2/*c*	*C*2/*c*
a (Å)	10.708 (2)	10.761(1)
b (Å)	9.3883(1)	9.4398(8)
c (Å)	39.82 (1)	40.064(4)
β ( )	94.668 (3)	94.598 (1)
V (Å^3)	3989.8(11)	4056.7(7)
Z, D_c (Mg/m^3)	4, 1.554	4, 1.522
μ	0.683	0.518
F(000)	1944	1932
Crystal size (mm)	0.34 x 0.28 x 0.12	0.33 x 0.23 x 0.13
Theta range for data collection ( )	2.05～25.10	2.04～25.10
Limiting indices	$-11\leqslant h\leqslant 12$; $-8\leqslant k\leqslant 11$; $-47\leqslant l\leqslant 44$	$-12\leqslant h\leqslant 12$; $-7\leqslant k\leqslant 11$; $-47\leqslant l\leqslant 46$
Absorption correction	Multi-scan	Multi-scan
Reflections collected	9788	9877
Unique data (R_{int})	3561 (R_{int} = 0.0283)	3610 (R_{int} = 0.0241) 99.9%
Max. and min. transmission	0.9220 and 0.7986	0.9376 and 0.8483
Refinement method	Full-matrix least-square on F^2	Full-matrix least-square on F^2
Data/restraints/parameters	3561 / 10 / 310	3610 / 10 / 311
S	1.047	0.985
Final *R* indices ($I > 2\sigma(I)$)	R = 0.0407, wR = 0.1077	R = 0.0322, wR = 0.0717
R indices (all data)	R = 0.0537, wR = 0.1169	R = 0.0418, wR = 0.0772
Largest diff. peak and hole (e/Å^3)	0.344 and –0.710	0.197 and –0.283

2. 5 In vitro anti-proliferative activities

2. 5. 1 Cell culture

The leukemic cells K562 and human lung cancer cells A549 were incubated with a RPMI-1640 medium. The number of tumor cells is 5×10^3 cells per hole in 96-well plate, the tumor cells continued to incubate for 24 h at 37 ℃, and the air in the incubator is humid air with 5% CO_2.

2. 5. 2 Antitumor activity evaluation

DMSO (two methyl sulfoxides) solutions of compounds **1**～**3** were prepared for reserve. When the cells were incubated for 24 h, the solution of each compound was added to each pore of the 96-well plates, and the concentration of each compound was 5, 10, 20, 40 and 80 μmol/L, respectively. After incubating for 48 hours, 10 μL of 5 mg/mL MTT solution was added to each hole. The tumor cells continued to incubate for 4 h at 37 ℃. The air in the incubator is humid air with 5% CO_2. 150 μL DMSO was added to each hole and the solution was clarified after shaking for 10 min. The absorbance of each pore sample was measured by microplate reader. IC_{50} was analyzed by IBM-SPSS (19.0) software.

3 RESULTS AND DISCUSSION

3. 1 Spectroscopic properties for 1～3

In the IR spectra of **1,** the broad absorption band at 3465 cm^{-1} is assigned for hydroxyl. The stretching vibration of carbonyl appears as a strong band at 1646 cm^{-1}. The bands due to the aromatic system occur near 1607, 1487 and 1447 cm^{-1}. The strong absorption bands at 1095 and 1052 cm^{-1} are correlated to sulfonate group, which is consistent with the literature[14]. The out-of-plane wagging vibrations for the aromatic system are observed at 899, 870, 771 and 687 cm^{-1}. The stretching vibration of C–O is shown at 1205 and 1144 cm^{-1} as strong band. The IR result proves that the sulfonate group was introduced into the tectochrysin molecule. As to the IR spectrum of **2** and **3**, they are similar to that of **1** because they have the same flavone skeleton.

In the ^1H NMR spectra of **1**, chemical shift at 13.15 ppm belongs to the proton of hydroxyl (C5–OH), and its chemical shift is higher than the normal value, which is due to the existence of O–H···O hydrogen bond between oxygen atom from carbonyl (C(4)=O) and hydrogen atom from hydroxyl (C(5)–OH). Compared with the ^1H NMR of tectochrysin[15] and chrysin[16], the peak due to the proton of tectochrysin's ring A (C(6)–H) disappears. This change indicates that the sulfonate group was introduced into the C(6) position of ring A.

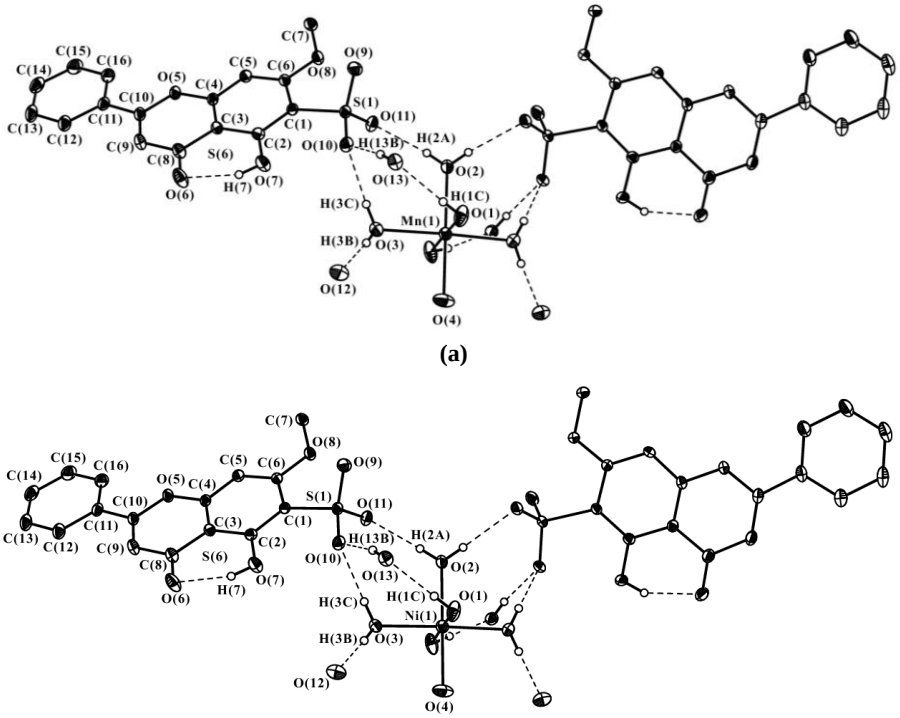
3. 2 Description of the molecular structures of 2 and 3

Table 2. Selected Bond Lengths (Å) of 2 and 3

Bond	Dist.	Bond	Dist.

2	Ni(1)−O(1)	2.041(2)	Ni(1)−O(1)$^{\#}$	2.041(2)
	Ni(1)−O(2)	2.060(4)	Ni(1)−O(4)	2.008(4)
	Ni(1)−O(3)	2.055(2)	Ni(1)−O(3)$^{\#}$	2.055(2)
	S(1)−O(9)	1.446(2)	S(1)−O(10)	1.448(2)
	S(1)−O(11)	1.458(2)		
3	Mn(1)−O(1)	2.1542(18)	Mn(1)−O(1)$^{\#}$	2.1542(18)
	Mn(1)−O(2)	2.179(3)	Mn(1)−O(4)	2.117(3)
	Mn(1)−O(3)	2.1761(17)	Mn(1)−O(3)$^{\#}$	2.1761(17)
	S(1)−O(9)	1.4481(16)	S(1)−O(10)	1.4454(15)
	S(1)−O(11)	1.4577(15)		

Symmetry code: (#) 1−*x*, *y*, 1/2−*z*



(a)

(b)

Fig. 1. Molecular structure of 2 (a) and 3 (b), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 25% probability level. The dashed lines indicate hydrogen bonds

2 or **3** consists of a metal cation $[Ni(H_2O)_6]^{2+}$ or $[Mn(H_2O)_6]^{2+}$, two 5-hydroxyl-7-methoxyflavone-6-sulfonate anions, six coordinated water molecules and four latticed water molecules. The molecular structures of **2** and **3** are shown in Fig. 1. The metal cation $[Ni(H_2O)_6]^{2+}$ or $[Mn(H_2O)_6]^{2+}$, lying on an inversion center, has a slightly distorted octahedral environment and is coordinated by six O atoms from coordinated water molecules. Four coordinated water molecules lie in the equatorial plane and the other two coordinated water molecules occupy the axial sites. The Ni–O distances (Table 2) are almost the same as the equivalent Ni–O distances in $[Ni(H_2O)](C_{16}H_{11}O_4SO_3)_2 \cdot 10H_2O$[17]. The Mn–O distances (Table 2) are in agreement with the literature[18]. Bond distances and angles of flavone skeleton agree with those of tectochrysin[19]. In the flavone skeleton of **2** or **3**, the benzopyrane ring consists of rings A (C(1)～C(6)) and C (C(3)～C(4)/O(5)/C(8)～C(10)). The dihedral angle between rings A and C is 1.99 °in **2** and 1.89 °in **3**, and that of the benzopyrane ring and ring B (C(11)～C(16)) is

1.39 º in **2** and 1.41 º in **3**, similar to the value found in tectochrysin[19]. The flavone skeleton is essentially planar, with the mean deviation from the mean plane being 0.021 Å for **2** and 0.020 Å for **3**. The similar S–O distances involving O(9), O(10) and O(11) show that the negative charge is delocalized over the three oxygen atoms in **2** and **3** (Table 2).

3. 3 Supramolecular interactions in 2 and 3

3. 3. 1 Hydrogen bonds

Sulfonate groups, coordinated water molecules and latticed water molecules in **2** or **3** are linked by O–H ··O hydrogen bonds (Fig. 1). The hydrogen atoms from coordinated water molecules with the oxygen atoms of sulfonate group form O(3)–H(3C) ··O(10) and O(2)–H(2A) ··O(11) hydrogen bonds. One interesting structural feature of **2** or **3** is the formation of a hydrogen bonding chain between sulfonate group and coordinated water molecule, which is mediated by a latticed water molecule. It contains O(13)–H(13B) ··O(10) and O(1)–H(1C) ··O(13). O(10) is involved in a three-centred hydrogen bond with H(13B) and H(3C), which includes O(13)–H(13B) ··O(10) and O(3)–H(3C) ··O(10). Hydrogen bond O(3)–H(3B) ··O(12) exists between coordinated water molecule and latticed water molecule. An independent O(7)–H(7) ··O(6) intramolecular hydrogen bond forms an intramolecular motif S(6) (Fig. 1). Besides the hydrogen bonds described above, another six kinds of classic O–H ··O hydrogen bonds exist in **2** or **3**. Details of the hydrogen bonds and hydrogen bonding geometry are given in Table 3. The extensive array of hydrogen bonds makes this region hydrophilic (Fig. 3).

Table 3. Hydrogen Bonding Geometry of 2 and 4 (Å, º)

	D–H ··A	d(D–H)	d(H ··A)	d(D ··A)	∠DHA
2	O(1)–H(1B) ··O(9)^{i}	0.81(3)	2.02(3)	2.806(3)	164(3)
	O(1)–H(1C) ··O(13)	0.79(3)	1.95(3)	2.741(4)	178(3)
	O(2)–H(2A) ··O(11)	0.81(3)	2.06(3)	2.859(3)	173(4)
	O(3)–H(3B) ··O(12)	0.82(4)	1.93(4)	2.743(4)	174(4)
	O(3)–H(3C) ··O(10)	0.81(3)	1.98(3)	2.774(3)	165(4)
	O(4)–H(4A) ··O(13)^{ii}	0.80(3)	1.94(4)	2.721(3)	164(4)
	O(7)–H(7) ··O(6)	0.82	1.80	2.543(3)	151
	O(12)–H(12B) ··O(11)^{iii}	0.80(3)	2.23(3)	3.010(4)	166(6)
	O(12)–H(12C) ··O(9)^{iv}	0.81(2)	2.101(19)	2.894(3)	166(4)
	O(13)–H(13B) ··O(10)	0.79(3)	2.04(3)	2.826(3)	169(4)
	O(13)–H(13C) ··O(8)^{iii}	0.80(4)	2.57(4)	3.111(3)	127(3)
	O(13)–H(13C) ··O(11)^{iii}	0.80(4)	2.06(4)	2.813(3)	156(4)
3	O(1)–H(1B) ··O(9)^{i}	0.81(2)	1.99(2)	2.793(3)	171(2)
	O(1)–H(1C) ··O(13)	0.81(3)	1.95(3)	2.752(3)	170(3)
	O(2)–H(2A) ··O(11)	0.81(3)	2.05(3)	2.856(2)	174(3)
	O(3)–H(3B) ··O(12)	0.84(3)	1.91(3)	2.747(3)	177(3)
	O(3)–H(3C) ··O(10)	0.84(2)	1.94(2)	2.773(2)	172(3)
	O(4)–H(4A) ··O(13)^{ii}	0.83(3)	1.90(3)	2.716(2)	173(2)
	O(7)–H(7) ··O(6)	0.82	1.80	2.543(2)	151
	O(12)–H(12B) ··O(11)^{iii}	0.81(3)	2.23(3)	3.010(3)	164(4)
	O(12)–H(12C) ··O(9)^{iv}	0.82(2)	2.079(19)	2.890(2)	169(3)
	O(13)–H(13B) ··O(10)	0.81(2)	2.04(2)	2.852(2)	173(2)
	O(13)–H(13C) ··O(8)^{iii}	0.82(3)	2.55(3)	3.111(2)	127(2)
	O(13)–H(13C) ··O(11)^{iii}	0.82(3)	2.04(3)	2.805(2)	155(3)'

Symmetry codes: (i) −*x*+3/2, *y*+1/2, −*z*+1/2; (ii) *x*−1/2, *y*+1/2, *z*; (iii) *x*+1/2, *y*+1/2, *z*; (iv) *x*, *y*+1, *z*

3. 3. 2 *π*-*π* Stacking interactions

The flavone skeletons of **2** or **3** are arranged in an antiparallel fashion and stacked into columns by *π*-*π* stacking interactions. In **2** (Fig. 2), Cg1–Cg2$^{\#}$ is 3.552 Å, and a perpendicular distance (Cg1 on ring 2$^{\#}$) is 3.461 Å, where Cg1 is the centroid of benzopyrone ring of the flavone skeleton at (*x*, *y*, *z*) and Cg2$^{\#}$ is the centroid of benzene ring of the flavone skeleton at (1−*x*, −*y*, −*z*). Cg2–Cg1* is 3.622 Å, with a perpendicular distance (Cg2 on ring 1*) to be 3.419 Å, where Cg2 is the centroid of benzene ring of the flavone skeleton at (*x*, *y*, *z*) and Cg1* is the centroid of benzopyrone ring of the flavone skeleton at (1/2−*x*, 1/2−*y*, −*z*). *π*-*π* stacking interaction of **3** is the same as that in **2**. Cg1–Cg2$^{\#}$ is 3.529 Å, and a perpendicular distance (Cg1 on ring 2$^{\#}$) is 3.450 Å; Cg2–Cg1* is 3.608 Å and a perpendicular distance (Cg2 on ring 1*) is 3.410 Å. These values are close to those reported for typical aromatic *π*-*π* stacking interactions[20], indicating the presence of *π*-*π* stacking interactions in **2** or **3**. The *π*-*π* stacking interactions are packed along the [110] direction with flavone skeletons and link flavone skeletons into columns. *π*-*π* Stacking interactions make this region hydrophobic (Fig. 3).

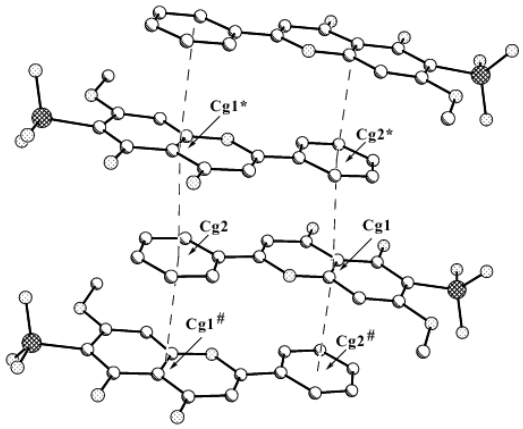


Fig. 2. Part of the crystal structures of 2 and 3, showing the π-π stacking interactions. Thin dashed lines indicate the *π*-*π* stacking interactions. Cg1 and Cg2 are the centroids of benzopyrone and benzene rings, respectively. Symmetry codes: (#) 1−*x*, −*y*, −*z*; (*) 1/2−*x*, 1/2−*y*, −*z*

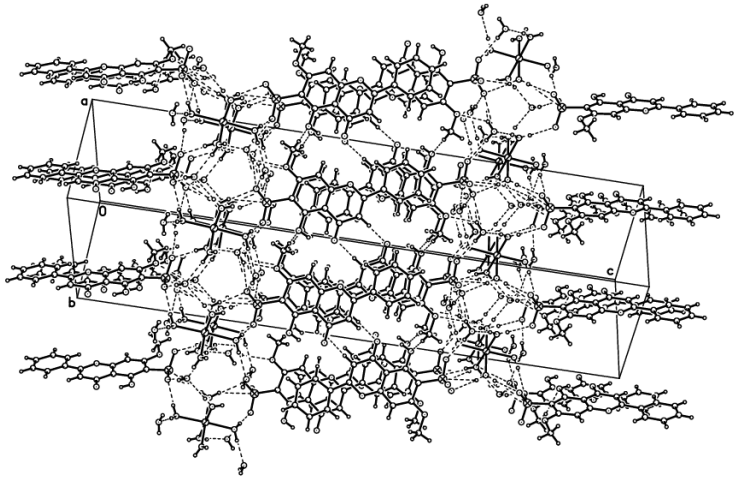


Fig. 3. Unit-cell packing diagram of 2 or 3

3. 4 Antitumor activity

Cisplatin was used as the positive control. The anti-proliferative activities *in vitro* against human leukemia cells K562 and human lung cancer cells A549 were evaluated by the standard MTT assay, and the inhibitory activity of tumor cell growth was expressed as the IC_{50} (Table 4). The pharmacological activity results showed that compounds **1**～**3** have anti-proliferative activity against human cancer cells K562 and A549. The antitumor activities of compounds **2** and **3** are stronger than that of **1**, which indicated that the introduction of sulfonic acid groups enhanced the antitumor activity of tectochrysin.

Table 4. Anti-tumor Activities of Compounds 1～3

Compound	K562 IC_{50} (μmol/L)	A549 IC_{50} (μmol/L)	Compound	K562 IC_{50} (μmol/L)	A549 IC_{50} (μmol/L)
1	18.3	19.3	**2**	18.8	21.6
3	19.5	20.7	Cisplatin	25.4	28.4

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Synthesis, Crystal Structure and Antitumor Activity of Tectochrysin-6-sulfonate

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Isomorphous crystals hexaquanickel(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate and hexaquamanganese(II) bis(5-hydroxyl-7-methoxyflavone-6-sulfonate) tetrahydrate were obtained. The crystal structures of them are organized into alternating hydrophilic and hydrophobic regions. The pharmacological activity results showed that these two compounds have anti-proliferative activity against human cancer cells K562 and A549.